group consisting of psoriasis area and severity index (PASI) and Target Lesion Assessment Score, wherein said baseline is the value established for said indicator in said patient by examining the patient within 60 days of administering the first dose of the soluble TNFα receptor.

23. A method of treating psoriasis comprising administering to a patient having psoriasis a therapeutically effective amount of TNFR:Fc, wherein said TNFR:Fc is administered in an amount and for a time sufficient to induce an improvement over baseline in an indicator selected from the group consisting of psoriasis area and severity index (PASI) and Target Lesion Assessment Score, wherein said baseline is the value established for said indicator in said patient by examining the patient within 60 days of administering the first dose of TNFR:Fc, and further wherein the TNFR:Fc is administered one or more times per week by subcutaneous injection for at least four weeks at a dose selected from the group consisting of 5-12 mg/m^2 of body surface area, 0.4 mg/kg of patient body weight, 25 mg per dose and 50 mg per dose. --

REMARKS

Claims 1-6, 8 and 11-13 are currently under consideration in the application and stand rejected under 35 U.S.C. § 112, second paragraph, and § 103. In the amendments set forth above, claim 2 has been cancelled, claims 1, 3-6, 8 and 11-13 have been amended and new claims 19-23 have been added to the application.

Claims 1, 12 and 13 have been amended by deleting the word "ordinary" from the phrase "ordinary psoriasis." In addition, claim 2 has been cancelled and its limitations added by amendment to claim 1. These changes are supported by cancelled claim 2 and also throughout the specification, for example, at page 19, line 16 to page 20, line 20; page 21, lines 7-9; page 21, line 26 to page 22, line 8; and in the example found at pages 22-27.

Claims 1, 12 and 13 also have been amended by adding language stating that the recipient of the treatment is a "patient having psoriasis." This language has been made to better express the intended meaning of the claims, and is believed to not affect the scope of these claims. This amendment is supported throughout the specification, for example, at page 19, line 16 to page 20, line 20; page 21, lines 7-9; page 21, line 26 to page 22 line 8; and in the example found at pages 22-27.

Claim 3 has been amended to change its dependency from cancelled claim 2 to claim 1, and to add language clarifying the intended meaning of the term "baseline." This amendment is supported in the specification, for example, at page 7, lines 8-12.

The amendments to claims 4, 5, 8 and 11 consist solely of amending their dependency from cancelled claim 2 to claim 1.

Claim 6 has been amended to change the phrase "5-12 mg/m^2" to read "5-12 mg/m^2 of body surface area." It is believed to be self-evident that "5-12 mg/m^2" in original claim 6 refers to m^2 of body surface area. Nonetheless, this amendment has been made to expedite the prosecution of this application. This change is believed to not effect the scope of claim 6, and is supported in the specification, for example, at page 22, lines 14-16.

Claim 12 has been amended to change the phrase "0.4 mg/kg" so that it now reads "0.4 mg/kg of patient body weight" and to change the phrase "25 mg" to instead read "25 mg per dose." It is believed that it was self-evident in original claim 12 that "0.4 mg/kg" referred to kg of patient body weight and that "25 mg" referred to 25 mg/dose. Nonetheless, to expedite prosecution of the application, the claim is now amended to read as indicated above. These changes are believed to not effect the scope of claim 12, and are supported in the specification, for example, at page 8, lines 31-37; page 9, lines 13-15; page 10, lines 8-9; and at page 22, lines 12-14.

New claims 19-21 are supported throughout the application, for example, at page 19, lines 26-36. New claims 22 and 23 are supported throughout the specification, for example, in claims 1 and 3 as originally filed, and at page 5, line 16 to page 7, line 19; page 21, line 26 to page 22, line 8; and in the example at pages 22-27.

In view of the foregoing comments, none of the amendments or new claims set forth above constitute the addition of new matter to the application.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The examiner has rejected claims 1, 12 and 13 on the basis that the phrase "ordinary psoriasis," which is recited in claim 1, renders these claims indefinite. The applicants disagree that this term is indefinite, as its meaning is clearly set forth in the specification at page 19, lines 26-36. The aforementioned text provides sufficient clinical detail to permit one skilled in the art to readily ascertain which patients are covered by the term "ordinary psoriasis." Nonetheless, to advance prosecution of this application, the term "ordinary psoriasis" has been replaced with "psoriasis" in claims 1, 12 and 13. Accordingly, the examiner is asked to withdraw this ground for the rejection of claims 1, 12 and 13.

Claim 3 has been rejected over the examiner's assertion that the term "baseline" was indefinite. To accommodate this concern, claim 3 has been amended as shown above to further clarify the intended meaning of the term "baseline." In view of this amendment the examiner is respectfully requested to remove this ground for the rejection of claim 3.

Claim 6 has been rejected over the examiner's assertion that the term "mg/m^2" is unclear. Applicants believe it is self-evident that "mg/m^2" refers to body surface

area and that this term therefore is clear in its meaning. However, to advance the prosecution of the application, claim 6 has been amended as suggested by the examiner to instead recite "mg/m^2 of body surface area." The examiner is accordingly asked to withdraw this ground for the rejection of claim 6.

Claim 12 is asserted to be indefinite over the examiner's belief that the term "mg/kg" is unclear. Applicants feel it is self-evident that "mg/kg" refers to kg of patient body weight and that this term therefore is clear. Nonetheless, to expedite the prosecution of the application, claim 12 has been amended as suggested by the examiner to instead recite "mg/kg of patient body weight." The examiner thus is requested to remove this basis for rejecting claim 12.

Claim 12 is further rejected over the examiner's view that the phrase "up to a maximum of 25 mg" is unclear. Though the applicants believe that this phrase in its original form is sufficiently clear, to further the prosecution of the application this phrase has been amended in accord with the examiner's suggestion to recite "up to a maximum of 25 mg/dose." The examiner therefore is asked to withdraw this ground for rejection of claim 12.

In view of the amendments discussed above, the claims are believed to be in accord with the requirements of 35 U.S.C.§ 112, second paragraph, and the examiner is respectfully requested to remove the rejections under this provision of claims 1, 3, 6, 12 and 13.

Rejections under 35 U.S.C. § 103

Rejections over combination of Barnes, Moreland, Mandell and Jacobs

Claims 1-6, 12 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Barnes (u13), Moreland (v13), U.S. Patent No. 4,965,271 (Mandell) and U.S. Patent No. 5,605,690 (Jacobs). At pages 4-8 of Paper No. 13, the examiner summarizes what he considers to be the pertinent teachings in each of these references and gives his reasons for concluding that this combination renders the rejected claims obvious.

To constitute a *prima facie* case of obviousness, teachings found in the cited references: (i) must contain some suggestion that would have motivated the skilled artisan to modify or combine the references; (ii) the proposed modification must have a reasonable expectation of success; and (iii) the references much teach or suggest all the limitations of the claims. These must be found in the references themselves, and may not rely on hindsight based on the applicants' own disclosure. In Paper No. 13 the examiner has acknowledged that none of the cited references teach the treatment of psoriasis with TNFR:Fc.

At pages 4-5 of Paper No. 13, the examiner discusses Barnes et al., a paper that reviews the role of NF-κB in chronic inflammatory diseases. Here the examiner asserts, *inter alia*, that Barnes teaches that "the activation of NF-κB therefore leads to a coordinated increase in the expression of many genes whose products mediate inflammatory and immune responses," that "[t]he production of interleukin-1, TNF-α, interleukin-6, granulocyte-macrophage colony-stimulating factor, and many chemotactic cytokines (chemokines) is increased in patients with asthma, rheumatoid arthritis, psoriasis and inflammatory bowel disease." Regardless of the foregoing assertions, Barnes et al. does not state that psoriasis can be ameliorated by inhibiting TNFα or any of the other cytokines or chemokines that may be elevated in these patients. In fact, the teachings of this reference suggest the possibility that to effectively treat psoriasis one might need to simultaneously inhibit several different cytokines, chemokines, and other kinds of molecules.

In characterizing Moreland et al., the examiner asserts, *inter alia*, that Moreland teaches that in rheumatoid arthritis patients, " [t]reatment with TNFR:Fc led to significant reductions in disease activity." However, Moreland et al. does not mention psoriasis and does not suggest that diseases other than rheumatoid arthritis should be treated using the therapeutic regimen described therein.

The examiner notes that Mandell et al. teaches that "psoriasis is among the conditions that can be treated or alleviated by the inhibition of IL-1, TNFα, and other leukocyte derived cytokines," and refers for support to the paragraph bridging columns 7-8 of this reference. Mandell et al. discloses xanthine compounds whose physiological activities include modulating the effects of leukocyte-derived cytokines on phagocytes, enhancement of chemotaxis, blocking the adherence of cells, modulating respiratory burst in stimulated PMNs and modulating the effects of cytokines on degranulation in stimulated phagocytes (column 7, lines 43-55). Mandell et al. does not teach or remotely suggest that one should substitute the xanthine compounds disclosed therein with any other therapeutic agent. The teachings of this reference are not consistent with the expectation that TNFR:Fc would be a suitable substitute. To the contrary, Mandell et al. emphasizes that the disclosed xanthine compounds are effective because they inhibit multiple targets, i.e. because they target "IL-1, TNF *and* other leukocyte derived cytokines" (emphasis added) (see e.g., column 1, lines 56- 60 and 64-68; column 2, lines 17-20 and 55-58; column 3, lines 29-33 and 48-53; column 7, lines 55-58, column 8, lines 59-61, etc.). Mandell defines "other cytokines" very broadly, (see column 3, lines 3-10), thus, Mandell et al. teaches that psoriasis can be treated by administering an inhibitor with a broad scope of inhibitory activity. One following the teachings of this reference

would not expect a substitute that has a narrower scope of inhibitory activity to be successful. Thus, Mandell et al. teaches away from such a substitution.

Jacobs is cited for teaching that "purified soluble TNFR protein is administered to a patient...for treatment of arthritis" (Paper No. 13, page 7). Jacobs does not mention psoriasis.

In justifying the motivation to combine these references, the examiner asserts at pages 6-7 of Paper No. 13 not only that "psoriasis is among the conditions that can be treated or alleviated by the inhibition of TNF," but asserts also that in various conditions including psoriasis "several cytokines recruit activated immune and inflammatory cells to the site of lesions, thereby amplifying and perpetuating the inflammatory state, the production of TNF-α is increased in patients with psoriasis, TNF-α has an important role in the inflammatory process, the treatment of patients with rheumatoid arthritis with antibodies to TNF-α can control refractory disease, and TNFR:Fc is safe and efficacious for the neutralization of TNF-α and the treatment of disease." The applicants respectfully protest that this string of assertions does not lead to the conclusion that it is obvious under 35 U.S.C. § 103 in view of these cited references to treat psoriasis with TNFR:Fc. First, as explained above, none of the cited references teach that psoriasis can be treated or alleviated by the inhibition of TNFα. Second, the cited references teach that several other cytokines and molecules in addition to TNFα are elevated in these patients (see above discussion of Barnes et al. and Mandell et al.), thus suggesting that treatment of this disease might require a pleiotropic agent or the simultaneous administration of several therapeutic agents. In this sense, these references teach away from the present invention. Third, though some of the cited references teach that arthritis can be treated with TNFα inhibitors, they do not teach or suggest that this same treatment would constitute an effective treatment for psoriasis. The examiner has not illustrated that one skilled in the art relying on those four references and unaware of the present disclosure would have been motivated to combine the teachings of these references to reach the methods taught herein, nor that if they did they would expect these methods to be successful.

The appropriate standard for combining a group of references under 35 U.S.C. § 103 was recently restated by the Federal Circuit in *In re Lee* (61 USPQ2d 143 (2002); copy attached as Exhibit A). In *In re Lee*, the examiner had rejected the claims as obvious over the combination of a U.S. patent describing a television menu display and the manual for a video game, stating that one skilled in the art would have been motivated to combine these teachings because the element extracted from the video game manual could "be used in many different devices," and was "user friendly and function[ed] as a tutorial." The Board of Patent Appeals and Interferences had

approved the examiner's reliance on "common sense," and had held that a "specific hint or suggestion" of motivation to combine was not required (*In re Lee* at page 1432). The Federal Circuit disagreed, stating that "the factual question of motivation is material to patentability and could not be resolved on subjective belief and unknown authority" (*In re Lee* at 1434). The court cited numerous similar holdings from its past decisions and added further that the Board's "[o]mission of a relevant factor required by precedent is both legal error and arbitrary agency action" (*Id*).

In the present case, the examiner has cited Barnes, Moreland, Mandell and Jacobs but has not shown that these publications contain specific suggestions that would instigate the combination of their teachings. Thus, in view of *In re Lee* the examiner has not provided a sufficient motivation to combine this group of references. There is no evidence that one skilled in the art, without the advantage of hindsight gleaned from the present disclosure, would have been motivated to piece together these four references. Mandell et al., for example, teaches the use of pleiotropic xanthine compounds for treating psoriasis, while Moreland et al. teaches the use of TNFR:Fc to treat rheumatoid arthritis. However, Mandell et al. does not teach or remotely suggest that one should treat psoriasis by substituting a different therapeutic agent for the xanthine compounds, nor does Moreland et al. suggest that a different disease should be substituted for rheumatoid arthritis. Barnes et al. mentions that several cytokines, including TNFα, are elevated in psoriasis, but does not describe any treatment for this condition. Jacobs et al. does not even mention psoriasis. Without the advantage of hindsight, there is no apparent reason why one skilled in the art would have been motivated to combine the teachings of this group of four references as proposed by the examiner.

In light of the foregoing comments, applicants believe that the examiner has not made a *prima facie* case that claims 1-6, 12 and 13 are obvious under 35 U.S.C. § 103(a) over the combination of Barnes, Moreland, Mandell and Jacobs.

In addition to the reasons set forth above, one skilled in the art would not expect TNFR:Fc to be effective for ameliorating psoriasis in view of two publications that were not cited by the examiner. At least two groups have reported that psoriasis can be beneficially treated by administering TNFα to patients who have psoriasis (Creaven et al., *J Am Acad Dermatol* 24:735-37 (1991); and Takematsu et al., *Br J Dermatol* 124:209-210 (1991); copies of these articles were provided with the Information Disclosure Statement submitted in this application on December 13, 2000). These papers describe the resolution of psoriatic lesions following the administration of TNFα to psoriasis patients. Clearly, these reports teach away from the methods claimed herein, which rely instead on the administration of an antagonist

of TNFα to treat this same condition. In view of Creaven et al. and Takematsu et al., one skilled in the art would consider the effectiveness of the disclosed treatments to be unexpected. Accordingly, the examiner is respectfully asked to remove the rejection of claims 1-6, 12 and 13 as being obvious under 35 U.S.C. § 103 in view of Barnes, Moreland, Mandell and Jacobs.

Rejections over combination of Barnes, Moreland, Mandell, Jacobs and Wallach

Claims 1, 2 and 11 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Barnes, Moreland, Mandell, Jacobs and Wallach. Claim 2 has been cancelled and its limitations added to claim 1.

At page 8 of Paper No. 13, the examiner states that Barnes, Moreland, Mandell and Jacobs "teach the administration of TNFR:Fc for the treatment of psoriasis, as discussed above." The applicants note that it is stated at pages 5-6 of Paper No. 13 that Barnes, Moreland and Mandell do not teach the treatment of psoriasis with TNFR:Fc. Jacobs et al. does not mention psoriasis. Accordingly, it appears that at page 8 of Paper No. 13 the examiner must have meant that the combination of Barnes, Moreland, Mandell and Jacobs rendered the invention of claims 1, 2 and 11 obvious, and not that these references literally "teach the administration of TNFR:Fc for the treatment of psoriasis."

The applicants have explained above why claims 1-6, 12 and 13 are not obvious over the combination of Barnes, Moreland, Mandell and Jacobs. No motivation to combine is found within this group of four references, the references fail to support an expectation of success for the present methods and furthermore, in view of the teachings of Creaven et al. and Takematsu et al., one skilled in the art would not expect TNFα inhibition to provide an effective treatment for psoriasis. The examiner characterizes Wallach as teaching "a controlled release pharmaceutical composition...having incorporated therein a soluble receptor capable of binding to its ligand" and that "[t]he soluble receptor is preferably the soluble form of TNF-α receptor." He asserts further that Wallach teaches that "[s]uch compositions are for use in the treatment of disorders in which neutralization of the deleterious effects of TNF-α is required."

The teachings of Wallach provide no reason that would motivate one skilled in the art to combine its teachings with Barnes, Moreland, Mandell and Jacobs nor does Wallach provide any reason why, in view of the above comments, one skilled in the art would expect the methods described in claims 1, 2 or 11 to be successful. Wallach teaches controlled release compositions that incorporate a soluble TNFα receptor, but does not teach or suggest that a soluble TNFα receptor would be effective for treating psoriasis. Accordingly, the examiner is respectfully requested to

withdraw the rejection of amended claim 1 as being obvious under 35 U.S.C. § 103 in view of the combination of Barnes, Moreland, Mandell, Jacobs and Wallach.

Claim 11, which depends from claim 1, specifies that the TNFR:Fc of claim 1 is administered in a sustained-release form. The invention of claim 11 includes all the limitations of amended claim 1. The applicants have explained above why amended claim 1 is not obvious over the combination of Barnes, Moreland, Mandell, Jacobs and Wallach. Accordingly, claim 11 also is not obvious in view of the combination of Barnes, Moreland, Mandell, Jacobs and Wallach. The examiner therefore is asked to remove this combination of references as a basis for the rejection of claim 11 under 35 U.S.C. § 103.

Rejections over combination of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman

Claims 1, 2 and 8 stand rejected as being obvious over the combination of Barnes, Moreland, Mandell, Jacobs, Pamukcu (b13) and Feldman (w13). It is explained above why amended claim 1 is not obvious over the combination of Barnes, Moreland, Mandell and Jacobs. Claim 8 depends from claim 1, thus incorporates the limitations of claim 1 and cannot be obvious unless claim 1 also is obvious.

Pamukcu, as characterized by the examiner, teaches "that phytochemotherapy (PUVA)...is used to treat moderate to severe psoriasis" and that PUVA "can be combined with other psoriasis therapies" (Paper No. 13, page 11). However, one skilled in the art would not combine PUVA with TNFR:Fc therapy without knowing that TNFR:Fc was a suitable treatment for psoriasis. As explained above, the combination of Barnes, Moreland, Mandell and Jacobs does not render it obvious that psoriasis can be ameliorated by administering, TNFR:Fc, and furthermore, Creaven et al. and Takematsu et al. teach away from the expectation that such a treatment would be effective. Pamukcu discloses small molecules for treating psoriasis, but does not mention TNFα and in fact states that the cause of psoriasis is unknown (column 1, lines 19-20). Even if the teachings of Pamukcu are added to the combination of Barnes, Moreland, Mandell and Jacobs, this further teaching does not strengthen the examiner's contention that the combination of Barnes, Moreland, Mandell and Jacobs renders it obvious to treat psoriasis with TNFR:Fc as described in amended claim 1. Thus, amended claim 1 is not obvious in view of the combination of Barnes, Moreland, Mandell, Jacobs and Pamukcu.

As characterized by the examiner, Feldman et al teaches "that the most effective therapy in inflammatory diseases will come from therapy aimed at several points in the disease pathway" (Paper No. 13, page 11). Feldman does not mention psoriasis and sheds no light on which points in the pathway of psoriasis are addressed by any therapy used to treat this disease. Thus, the combination of Barnes, Moreland,

Mandell, Jacobs, Pamukcu and Feldman does not render obvious the invention described in amended claim 1. Accordingly, the examiner is respectfully requested to remove the combination of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman as a ground for the rejection of amended claim 1 under 35 U.S.C. § 103.

Claim 8 stands rejected over the combination of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman. Claim 8 specifies that the treatment of claim 1 is administered concurrently with phototherapy/ultraviolet light B, psoralen/ultraviolet light A ("PUVA"), plasmapheresis or sunbathing. As explained above, amended claim 1 is not obvious over the combination Barnes, Moreland, Mandell, Jacobs and Pamukcu. Since claim 8 incorporates all the limitations of amended claim 1, claim 8 also is not obvious over this combination of references. None of these six references, alone or taken together, teach or suggest that TNFR:Fc is an effective treatment for psoriasis. The examiner therefore is asked to remove the combination of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman as a ground for the rejection of claim 8 under 35 U.S.C. § 103.

Obviousness-type Double Patenting

According to MPEP § 804.II.B.1, before issuing an obviousness-type double patenting rejection, it should be determined whether the application claims an invention that is "merely an obvious variant" of an invention claimed in the patent. The patent is not to be treated for this purpose as "prior art," and only the patented claims over which the rejection is issued and those parts of the disclosure supporting those claims are to be used for this analysis. Section 804.II.B.1 instructs further that this determination must employ the same factual inquiries set forth in Graham v. John Deere, and that any obviousness-type double patenting rejection must make clear not only the differences between the conflicting claims but also the reasons why a person of ordinary skill in the art would conclude that the claim at issue is an obvious variation of the previously patented invention.

Nonstatutory double patenting rejection over claims 1-3 of U.S. 5,605,690 (Jacobs)

Claims 1-6, 8 and 11-13 stand rejected over claims 1-3 of U.S. Patent No. 5,605,690 (Jacobs) based on the judicially created doctrine of obviousness-type double patenting. Claims 1-3 of Jacobs cover methods for "lowering the levels of active TNF-α in a mammal in need thereof" by administering a TNF antagonist. Claims 1-6, 8 and 11-13 pertain to methods for treating psoriasis that involve administering TNFR:Fc. Claim 2 has been cancelled and its limitations added by amendment to claim 1. The applicants respectfully traverse this rejection for the reasons given below.

In presenting his reasons for this rejection, the examiner has impermissibly ventured beyond the disclosure of Jacobs itself. At page 13, lines 1-4 of Paper No. 13, the examiner stated that "it would have been obvious...to lower the TNF-α levels in mammal wherein the mammal is a human and the human has psoriasis, *as evidenced by the prior art rejections of record*" (emphasis added). Thus, the obviousness-type double-patenting rejection in view of Jacobs taken alone is improperly supported because it relies in part on supplementary references. Accordingly, the obviousness-type double-patenting rejection based on Jacobs taken alone should be withdrawn.

Furthermore, earlier portions of Paper No. 13 suggest that the examiner does not consider the subject claims to be obvious over Jacobs taken alone. At pages 4-12 of Paper No. 13, the examiner rejected the claims under 35 U.S.C. § 103 over three different combinations of references, all of which included Jacobs. However, in this section of Paper No. 13, he did not reject any claim as being obvious over Jacobs taken alone. The absence of such a rejection suggests that the examiner does not consider the subject claims to be obvious over Jacobs taken by itself.

If one applies the analysis described in MPEP § 804.II.B.1, it is apparent that the invention claimed in claims 1-6, 8 and 11-13 herein are not an "obvious variant" of the invention of claims 1-3 of Jacobs. Even if the examiner's improper reliance on supplementary references is overlooked, the reasons he offered to justify this rejection do not support a conclusion that claims 1-6, 8 and 11-13 are an obvious variant of claims 1-3 of Jacobs.

The examiner asserted, for example, that "lowering the levels of TNFα in a mammal covers the administration of TNFR:Fc to treat psoriasis" (Paper No. 13, page 12, lines 25-27). Here, the examiner takes aim at the wrong target by focusing on whether the claims in the earlier patent *dominate* the subject claims. MPEP 804.II. states:

> *Domination and double-patenting should not be confused. They are two separate issues. One patent or application "dominates" a second patent or application when the first patent or application has a broad or generic claim which fully encompasses or reads on an invention defined in a narrower or more specific claim in another patent or application. Domination by itself, i.e., in the absence of statutory or nonstatutory double patenting grounds, cannot support a double patenting rejection.... However, the presence of domination does not preclude double patenting.*

In further warning against equating obviousness and dominance, MPEP § 804.II.B.2 quotes from *In re Kaplan* (789 F.2d 1574 (Fed. Cir. 1986)), stating that "the mere fact that the broad process claim of the patent...reads on or 'dominates' the narrower

claim...does not, per se, justify a double patenting rejection." It is long-established that a species may be patentable even in instances where the genus to which the species belongs is previously known. The analysis here should focus not on whether claims 1-3 of Jacobs "cover" the subject claims, but on whether or not the present claims represent an obvious variation of the methods set forth in claims 1-3 of Jacobs. Claims 1-3 of Jacobs relate to methods for "lowering TNFα levels in a mammal in need thereof," while the subject claims pertain to methods for ameliorating psoriasis. The examiner has not provided evidence that the latter is an obvious variant of the former.

According to the MPEP, the analysis for a double-patenting obviousness rejection "parallels the guidelines for a 35 U.S.C. § 103 rejection" (MPEP § 804.II.B.2). Thus, the present analysis should apply the usual criteria for determining a *prima facie* case of obviousness. This includes asking whether claims 1-3 and the supporting portions of the specification of Jacobs contain some suggestion that would have motivated the skilled artisan to modify that disclosure to reach the present invention; whether these portions of Jacobs engender a reasonable expectation of success for the modified method; and whether claims 1-3 of Jacobs teach or suggest all the limitations of the rejected claims.

When the proper analysis is performed, it is apparent that the present claims are not an obvious variant of the invention of the invention described in claims 1-3 of Jacobs. One requirement for a *prima facie* case of obviousness is that all of the elements in the rejected claims must be present in the cited reference. The examiner asserts in the sentence bridging pages 12-13 of Paper No. 13 that "psoriasis is a species of ailment of the genus of ailments caused by elevated TNF-α levels." However, Jacobs does not teach or suggest that psoriasis is an ailment caused by elevated TNFα levels. Jacobs does not even mention psoriasis. Identifying a psoriasis patient as the target for treatment is an essential element of the methods of rejected claims 1-6, 8 and 11-13. This element not only is absent from claims 1-3 of Jacobs, but from the perspective of one skilled in the art, this element is not obvious in view of the Jacobs disclosure. As discussed above, Creaven et al. and Takematsu et al. have reported the successful treatment of psoriasis by administering TNFα. In view of these reports, one following the teachings of Jacobs would not reasonably expect that psoriasis could be effectively treated by administering TNFR:Fc to a psoriasis patient. Thus, the subject claims do not describe an "obvious variant" of the invention described in claims 1-3 of Jacobs. For this and for the other reasons set forth above, the examiner is respectfully asked to withdraw the obviousness-type double patenting rejection of claims 1-6, 8, and 11-13 to the extent that this rejection is based on Jacobs taken alone.

Nonstatutory obviousness-type double patenting rejection over claims1-3 of Jacobs in view of Barnes, Moreland, Mandell and Jacobs

Claims 1-6, 12 and 13 are further rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of Jacobs in view of Barnes, Moreland, Mandell and Jacobs (Paper No. 13, page 13). Claim 11 was not included in this rejection. As noted above, since Jacobs is the patent on which this rejection is based, only claims 1-3 and the supporting disclosure of this patent, not Jacobs in its entirety, should be considered here in combination with Barnes, Moreland and Mandell.

In explaining his reasons for this rejection, the examiner relies on arguments similar to those used to support rejections under 35 U.S.C. § 103 based on these same references. However, this type of rejection requires a showing that the rejected claims represent an obvious variant of the earlier claims. No such showing has been made in the present case.

As explained above in rebutting the rejections under 35 U.S.C. § 103, the subject claims are not obvious over the combination of Barnes, Moreland, Mandell and Jacobs. For example, the examiner has not provided evidentiary support for his statement that "psoriasis is a species of ailment of the genus of ailments caused by elevated TNF-α levels" (pages 12-13 of Paper No. 13). Among this group of references, only Barnes and Mandell even mention psoriasis, and both teach that psoriasis patients exhibit elevated levels of several different cytokines and other kinds of molecules. Neither of these references teach that elevated TNFα is the *cause* of psoriasis nor that this disease could be ameliorated by inhibiting TNFα. Furthermore, those skilled in the art would be aware that according to Creaven et al. and Takematsu et al., psoriasis can be treated by administering TNFα. Thus, they would not expect the method described in claims 1-3 of Jacobs to be useful for treating psoriasis and would not adapt that method for treating this disease. Accordingly, the combination of Barnes, Moreland, Mandell and Jacobs does not support the conclusion that the present invention is an obvious variant of claims 1-3 of Jacobs. The examiner therefore is requested to remove the rejection of claims 1-6, 12 and 13 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell and Jacobs.

Nonstatutory double patenting rejection over claims 1-3 of Jacobs in view of Barnes, Moreland, Mandel, Jacobsl and Wallach

Claims 1, 2 and 11 are alternatively rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell, Jacobs and Wallach. Claims 4-6, 12 and 13 are not included in this rejection. As explained above, only

claims 1-3 of Jacobs and supporting disclosure should be considered here, and not Jacobs in its entirety.

It is explained above under the heading of "Rejections under 35 U.S.C. § 103(a)" why the claims 1, 2 and 11 are not obvious under 35 U.S.C. § 103 in view of the combination of Barnes, Moreland, Mandell, Jacobs and Wallach. If these claims are not obvious in view of this combination of references, these same references do not show these same claims are an obvious variant of claims 1-3 of Jacobs.

Wallach teaches a controlled release composition that incorporates a soluble TNFα receptor, but does not teach or suggest that these compositions should be used to treat psoriasis. Wallach seems irrelevant to amended claim 1 because this claim does not specify a controlled release composition. Accordingly, the examiner is respectfully requested to withdraw the rejection of claim 1 under the nonstatutory doctrine of obviousness-type double patenting in view of the combination of Barnes, Moreland, Mandell, Jacobs and Wallach.

Claim 11 specifies that the TNFR:Fc of claim 1, administered to treat psoriasis, is in a sustained-release form. Claim 11 depends from claim 1, thus incorporates all of the latter's limitations and cannot be obvious unless claim 1 also is obvious. The cited combination of references, including Wallach, does not support the examiner's assertion that "psoriasis is a species of ailment of the genus of ailments caused by elevated TNF-α levels." The teachings of Creaven et al. and Takematsu et al., discussed above, suggest to the contrary that elevated levels of TNFα would be beneficial to a psoriasis patient. Furthermore, another reference cited by the examiner states that the cause of psoriasis is unknown (Pamukcu, column 1, lines 19-20). None of the references cited here support the expectation that TNFR:Fc, regardless of how it is administered, would be an effective treatment for psoriasis. Accordingly, the combination of Barnes, Moreland, Mandell, Jacobs and Wallach fails to establish that the method of claim 11 is an obvious variant of the invention described in claims 1-3 of Jacobs. The examiner therefore is respectfully requested to withdraw the rejection of claim 11 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell, Jacobs and Wallach.

Nonstatutory double patenting rejection over claims1-3 of Jacobs in view of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman

Claims 1, 2 and 8 are alternatively rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell and Jacobs and further in view of Pamukcu and Feldman. Claims 4-6 and 11-13 are not included in this rejection. As explained

above, only claims 1-3 of Jacobs and the disclosure supporting these claims should be consulted for this analysis. Claim 8, which depends from claim 1, specifies that the TNFR:Fc-treated psoriasis patient is treated concurrently with PUVA, phototherapy with ultraviolet light B, plasmapheresis or sunbathing.

The examiner justifies this rejection, for example, by reasserting that "lowering the levels of TNF-α in a mammal covers the administration of TNFR:Fc to treat psoriasis." As noted above, such assertions do not justify this rejection because the issue of whether the earlier claims dominate the present claims is not dispositive of whether an obviousness-type double patenting rejection is appropriate. Furthermore, in light of the results reported by Creaven et al. and Takematsu et al., one skilled in the art would not expect that lowering the levels of TNFα in a psoriasis patient would be an effective treatment for this condition and therefore would not be motivated to modify claims 1-3 of Jacobs to reach the invention described in amended claim 1.

As the applicants noted above in discussing the rejections under 35 U.S.C. § 103, the combination of Moreland, Mandell and Jacobs, even if Pamukcu and Feldman are added to the combination, does not suggest that psoriasis should be treated by administering TNFR:Fc. Even if such suggestion were present in this group of references, one skilled in the art would not reasonably expect such treatment to be successful in view of the results reported by Creaven et al. and Takematsu et al. Without knowing that psoriasis could be ameliorated by administering TNFR:Fc, one would not be motivated to combine the PUVA taught by Pamukcu with the TNFR:Fc treatments described in amended claim 1.

Feldman et al. teaches that inflammatory diseases are more effectively treated by combining therapy aimed at several points in the disease pathway, but does not discuss any therapy for treating psoriasis, let alone elucidate which points in the disease pathway each treatment attacks. Thus, the combination of Pamukcu, Feldman, Barnes, Moreland, Mandell and Jacobs does not render it obvious to modify claims 1-3 of Jacobs by specifying a psoriasis patient as the recipient of the therapeutic agent. Accordingly, the examiner is asked to withdraw the rejection of claim 1 under the judicially created doctrine of obviousness-type double patenting in view of claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman.

Claim 8 also is rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-3 of Jacobs taken together with Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman. Because claim 8 depends from claim 1 and thereby incorporates the limitations of claim 1, the above comments apply also to claim 8. Since claim 1 does not describe an obvious variant of claims 1-3 of

Jacobs, claim 8 also does not describe an obvious variant of the invention of claims 1-3 of Jacobs. The examiner therefore is respectfully requested to remove the rejection of claim 8 over claims 1-3 of Jacobs in view of Barnes, Moreland, Mandell, Jacobs, Pamukcu and Feldman.

The above remarks illustrate that claims 1-6, 8 and 11-13 do not describe obvious variants of the invention set forth in claims 1-3 of Jacobs, even when Jacobs is considered in view of one or more of the other references cited here by the examiner. Accordingly, these remarks demonstrate that the requirement for a terminal disclaimer is not warranted, and the examiner therefore is asked to withdraw this requirement.

CONCLUSIONS

Claims 1, 3-6, 8, 11-13 and 19-23 are pending in the application, and claims 1, 3-6, 8 and 11-13 have been amended as indicated above. Claims 1, 3, 6, 12 and 13 have been rejected under 35 U.S.C. § 112, second paragraph. In view of the above comments and the amendments to claims 1, 3, 6, 12 and 13, the rejections under 35 U.S.C. § 112, second paragraph, are believed to be overcome. Claims 1-6, 8 and 11-13 stand rejected under 35 U.S.C. § 103 in view of various combinations of prior art publications cited by the examiner. It is shown above that the examiner has failed to make a *prima facie* case of obviousness based on these combinations of references and moreover that even had he done so, the amended claims still would not be obvious because there is prior art that teaches away from the present invention. The above comments show also that the nonstatutory obviousness-type double patenting rejections issued by the examiner are not justified and the examiner accordingly is respectfully requested to withdraw the requirement for a terminal disclaimer.

"When an applicant submits evidence traversing a rejection, the examiner must reconsider the patentability of the claimed invention. The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence" (M.P.E.P. § 716.01(d)). In view of the applicants' comments and arguments set forth above, it is believed that the totality of the record supports the patentability of the claims now under consideration in this application. Accordingly, claims 1, 3-6, 8, 11-13 and 19-23 are believed to be in condition for allowance and notification to that effect is respectfully requested.

The examiner is asked also to take note of the accompanying Petition for Correction of Inventorship. A timely response to this petition is hereby requested. If

the examiner has any further concerns in this application, he is asked to contact the undersigned at her direct dial number given below.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this Response to Office Action is being deposited with the United States Postal Service in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231.

October 22, 2002
Date

Elizabeth M. McCarthy

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Appendix to Response to Office Action filed October 22, 2002
(marked up version of claims amended by the attached Response to Office Action)

1. (Amended) A method of treating [ordinary] psoriasis in a human patient having psoriasis comprising administering to said patient a therapeutically effective amount of [a soluble TNF receptor] TNFR:Fc.

3. (Amended) The method of claim [2] 1, wherein said TNFR:Fc is administered in an amount and for a time sufficient to induce an improvement over baseline in an indicator selected from the group consisting of psoriasis area and severity index (PASI) and Target Lesion Assessment Score, wherein said baseline is the value established for said indicator in said patient by examining the patient within 60 days of administering the first dose of TNFR:Fc.

4. (Amended) The method of Claim [2] 1, wherein the TNFR:Fc is administered one or more times per week.

5. (Amended) The method of Claim [2] 1, wherein the TNFR:Fc is administered by subcutaneous injection.

6. (Amended) The method of Claim 5, wherein the patient is an adult and the amount of TNFR:Fc injected is 5-12 mg/m^2 of body surface area, 25 mg or 50 mg.

8. (Amended) The method of Claim [2] 1, wherein the TNFR:Fc is administered concurrently with a therapy selected from the group consisting of phototherapy with ultraviolet light B, psoralen combined with ultraviolet light A, plasmapheresis and sunbathing.

11. (Amended) The method of Claim [2] 1, wherein the TNFR:Fc is administered in a sustained-release form selected from the group consisting of TNFR:Fc that is encapsulated in a biocompatible polymer, TNFR:Fc that is admixed with a biocompatible polymer, and TNFR:Fc that is encased in a semi-permeable implant.

12. (Amended) A method of treating [ordinary] psoriasis in a pediatric human patient having psoriasis comprising administering to said patient a

therapeutically effective amount of TNFR:Fc, wherein the TNFR:Fc is administered by subcutaneous injection one or more times per week at a dose of 0.4 mg/kg of patient body weight, up to a maximum of 25 mg per dose.

13. (Amended) A method of treating [ordinary] psoriasis in an adult human patient having psoriasis comprising administering by subcutaneous injection to said patient a dose of 25 mg of TNFR:Fc two times per week for one or more weeks or a dose of 50 mg of TNFR:Fc one time per week or two times per week for one or more weeks.